REMARKS

Applicants thank the Examiner for entering the amendments filed in the response of August 22, 2003.

Claims 32-56 are in this application; no claims having been cancelled; and Claims 37, 41-49, 51 and 52 having been withdrawn.

In the Office Action mailed July 6, 2004, the Examiner maintained the restriction requirement as proper. In addition, the Examiner requested a list of co-pending and related cases. There are no co-pending or related patent applications.

Applicants thank the Examiner for withdrawing the rejection of Claims 32-40 as being drawn to an improper Markush group; for withdrawing the rejection of Claims 33-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention (page 3 of the Office Action); and for withdrawing the rejection of Claims 33-36 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention (bottom of page 3 to page 4 of Office Action).

On page 4 of the Office Action, the Examiner maintained the rejection of Claims 32-34, 38-40 and 53-56 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. According to the Examiner, "[t]he claims are directed to the preventing, reducing or eliminating side effects, or neutralizing the side effects, or a cancerostatic or immunosuppressive agent comprising administering a compound having PP activity. The specification provides support on page 110-115 for neutralization of the growth-inhibiting effect of an anti-tumor substance, K22.097, by administration of nicotinic acid or nicotinamide in human leukemia cells, in normal leukocytes, in primary intestine cells and in NMRI mice." The Examiner cited *In re Wands* for factors to consider when assessing whether a disclosure would require undue experimentation.

On page 6 of the Office Action, the Examiner further note that

> "the relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of oncology", that "each particular neoplastic or immunologic disease or disorder has its own specific characteristics and etiology. The unpredictability observed with single agent therapy is compounded when a combination of agents is employed." The broad recitation "preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent" is inclusive of many pathologies that presently have no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy."

The Examiner further summarizes the factors considered in *In re Wands*, noting that

"the claims are very broad and inclusive of any side effect of any cancerostatic or immunosuppressive agent comprising administering a plethora of disclosed compound having PP activity ... The working examples are limited ... The instant specification sets forth no such understanding or any criteria for extrapolating beyond the combination of the single anti-tumor substance K22.097 and nicotinamide or nicotinic acid ... no direction is provided to prevent or eliminate a side effect. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic combination to prevent or eliminate any particular side effect following administration of a cancerostatic or immunosuppressive agent, one skilled in the oncology or immunology art would have to test extensively many combinations of agents to discover which particular type of side effect responds to that particular combination. The specification provides inadequate guidance to do otherwise."

Applicants respectfully disagree with the Examiner's characterization of the disclosure in the present specification and the conclusions drawn therein.

Considering the *Wands* factors as recited in the Office Action:

1). The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

As described above, the nature of the invention is a method for preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent administered to a patient, comprising administering a compound having vitamin PP activity. The precise nature of the cancerostatic or immunosuppressive agent or the particular side effects cause by these agents is irrelevant to the method of the present invention, provided that the compound administered is a compound having vitamin PP activity as taught in the specification. The invention does not claim the identification nor the characterization of different side effects caused by the cancerostatic or immunosuppressive agent; nor does the invention claim the cancerostatic or immunosuppressive agents that may cause such side effects.

The test protocols described on pages 110 to 115 of the specification are but some of the well established methods for determining the ability for compounds, such as the vitamin PP compounds of the invention, to suppress the side-effects of anti-tumor agents. Therefore, the claimed method does not rely on heretofore generally unknown or undescribed research methods or techniques.

As noted by the Examiner, the relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the field of oncology. In addition, the experimental methods described above for determining the level of activity of a compound of the vitamin PP group for suppressing the side-effects of an anti-tumor substance, may also be performed and interpreted by a trained B.S. or M.S. level scientists in the field of biology or biochemistry. A person of ordinary skill in the art would have no difficulty, in view of the disclosure in the application and their knowledge, in carrying out the experiment.

While the examiner notes that each particular neoplastic or immunologic disease or disorder may have its own specific characteristics and etiology, the method claimed in the present invention is simply a method of preventing, reducing, eliminating or neutralizing the side effects of a cancerostatic or immunosuppressive agent by administering a vitamin PP compound. The inability to predict *a priori* the particular characteristics and etiology of a neoplastic or immunologic disease or disorder is irrelevant to the claimed method.

2). The breadth of the claims

As recited in Claim 32, the claimed invention is a method for preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent administered to a patient, comprising administering a compound having vitamin PP activity. The claim is narrowly drawn to this method only for preventing, reducing or eliminating side effects, and as noted above, does not depend on 1) the nature of cancerostatic or immunosuppressive agents, 2) the number of cancerostatic or immunosuppressive agents, and 2) the number of compounds having PP activity as disclosed in the specification. Thus, no matter how many type of side effects, the nature or number of cancerostatic or immunosuppressive agents that may be employed, or the nature or number of compounds having PP activity, the method recited in Claim 32 is still the same.

Claim 32 narrowly teaches a method for preventing, reducing, eliminating or neutralizing the side effects of a cancerostatic or immunosuppressive agent by administering a compound having vitamin PP activity (or a prodrug of the compound). As noted by the Examiner on page 4 of the Office Action, pages 110-115 of the specification provides detailed experimental support for the neutralization of the growth-inhibiting effect of antitumor agents by nicotinic acid and nicotinamide, both compounds of which are members of the vitamin PP group, demonstrated by using human leukemia cells (example 1), normal lymphocytes (example 2) intestine cells (example 3) and in NMRI mice (example 4). In addition, for example, pages 6-28 teaches the general classes of compounds and pages 28-33 teaches representative and specific compounds having vitamin PP activity.

3). The amount of direction or guidance provided and the presence or absence of working examples

As noted above and affirmed of page 6 of the Office Action by the Examiner, the four working examples teach the administration of the anti-tumor substance K22.97 and nicotinamide or nicotinic acid (as representative of vitamin PP compounds) in laboratory models using cells from a human monocytic leukemia, normal lymphocytes, crytic cells for the large intestine, and in NMRI mice.

4). The quantity of experimentation necessary

The specification teaches both general classes of compounds (pages 6 to 28) and also representative specific compounds (pages 28-33) having vitamin PP activity that may be used in the method of the claimed invention. The Examiner asserts on page 7 that "Applicants have failed to provide guidance as to which particular compound having PP activity in combination with which particular cancerostatic or immunosuppressive agent would be preferred for preventing, reducing or eliminating side effects or neutralizing which particular side effects." However, as emphasized above, Applicants' invention recite only a method of preventing, reducing or eliminating side effects; and the method does not depend on 1) the nature of cancerostatic or immunosuppressive agents, 2) the number of cancerostatic or immunosuppressive agents, and 2) the number of compounds having PP activity as disclosed in the specification. Thus, the method does not rely on the number or types of side effects, or the nature or number of cancerostatic or immunosuppressive agents that may be employed.

On page 7 of the Office Action, the Examiner asserted that while the specification supports neutralization of side effects,

> "no direction is provided to prevent or eliminate a side effect. Only neutralization under a specific set of conditions is clearly supported. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic combination to prevent or eliminate any particular side effect following administration of a cancerostatic or immunosuppressive agent, one skilled in the oncology or immunology art would have to test extensively many combinations of agents to discover which particular type of side effect responds to that particular combination. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise."

As noted above, the invention as claimed in Claim 32, is a method for preventing, reducing, or eliminating the side effects of a cancerostatic or immunosuppressive agent comprising administering to a patient a compound having vitamin PP activity or a prodrug thereof. Dependent Claim 33 further limits the method to the compounds of formulae II, IIa, IIb, III, IIIa, IIIb, IIIc, IV, IVa, IVb, V, Va, and Vb. The method relies on the discovery that

the compounds of this invention having vitamin PP activity prevent, reduce or eliminate the side effects of a cancerostatic or immunosuppressive agent.

Applicants dispute the Examiner's conclusion that "a particular combination of drugs in the treatment of a particular side effect to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent." Applicants concede that Applicants may not have explicitly named every side effects or every cancerostatic or immunosuppressive agents that may be employed, and perhaps there may be other cancerostatic or immunosuppressive agents that are not presently known. However, with due respect, whether there may be other cancerostatic or immunosuppressive agents that may induce a particular known or yet determined side effect is not the issue in considering the enablement issue of Claim 32 (and its dependent claims) without undue experimentation: the issue for enablement is whether it is reasonable to believe that, if the side effects caused by cancerostatic or immunosuppressive agents are treatable, then it will be treatable by the administration of compounds with vitamin PP activity as is claimed in Claim 32.

As the CCPA stated in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971), "A specification disclosure that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 USC 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." And "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumably accurate disclosure."

Here, the disclosure contains a teaching of the manner and process for preventing, reducing, eliminating or neutralizing the side effects of cancerostatic or immunosuppressive agents by administering a compound having vitamin PP activity, that is completely congruent with the scope of Claim 32, the broadest method of treatment claim in the present application. And, considering the detailed working Examples 1-4 on pages 110-115, which clearly demonstrates that "the cases of death caused by the anti-tumor substances as well as the strong reduction of leucocyte cells could be completely prevented" and that "the use of compounds of the vitamin PP group according to the invention is capable of suppressing the unavoidable side-effects of anti-tumor substances or is at least capable of elevating these and/or neutralizing the cancerostatic activity in a surprising manner in unexpected threatening incidents." See page 115 of the specification. The important point of the invention is not the particular nature or character of the side effects nor the particular cancerostatic or immunosuppressive agents that may be used, as the invention does not lie in the determination of the side effects or the type of agents that maybe employed, but only in a

method for preventing, reducing, eliminating or neutralizing the side effects of a cancerostatic or immunosuppressive agent using compounds having PP activity.

In addition, Applicants successfully elucidated the mechanism by which the compounds act on the human organism. See U.S Patent 6,506,572. In this patent, Applicants determined that the compounds especially inhibit the cellular formation of niacinamide mononucleotide; and by employing these compounds, many malignant cells are affected while non-malignant cells are unaffected. With respect to the activities of the agents acting on human and non-human malignant and non-malignant tumor cells, it may be presumed that their side effects are similar and the effects are caused by the same or similar mechanism of action. Therefore, the prevention, reduction or elimination of the side effects using the compounds of the present invention may be achieved by the same mechanism of action; i.e. by the administration of a compound having vitamin PP activity to the patient as disclosed in the present patent application.

Applicants respectfully submit that the specification provides all information needed for the person of ordinary skill in the art to practice the claims without undue experimentation, and that Claims 32-36, 38-40, and 50 are therefore enabled by the specification. Withdrawal of the rejection is requested.

On page 7 of the Office Action, the Examiner maintained her rejection of Claims 32-36 under 35 U.S.C. 102(a) as being anticipated by Budihardjo et al because the Examiner maintains that Budihardjo teaches the therapeutic administration of the nicotinamide derivative, 6-aminonicotinamide, which can be metabolized in vivo to a compound with vitamin PP activity.

Applicants maintain the previous assertion that Claim 32 in the present application claims a "method for preventing, reducing, or eliminating side effect or neutralizing the side effects of a cancerostatic or immunosuppressive agent" while Budihardjo teaches that 6-aminonicotinamide (6AN) increases the sensitivity of human cancer cells to cisplatin. See Budihardjo, p. 122, 2nd column. A disclosure of a method for increasing the sensitivity of cancer cells to cancerostatic agents is not the same as the teaching of a new method for preventing, reducing, eliminating or neutralizing the effects of cancerostatic or immunosuppressive agent by the administration of a compound having vitamin PP activity. Budihadjo clearly does not teach nor suggest the use of any agent to protect non-tumor cells, which is an important aspect of reducing the side effects of cancerostatic or immunosuppressive agents such as cisplatin therapy as taught in the present invention.

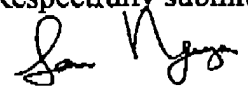
The Examiner further reasserts the speculation that "as a "modulator of the action of various antineoplastic treatments", it would have been reasonable to expect any number of functional and morphological cellular changes would occur that alter in a positive way the

side effect profile of a cancerostatic or immunosuppressive agent." However, nowhere does Budihardjo teach the method of the present invention as recited in Claim 32.

The Examiner maintained her rejection of Claims 32-36 under 35 U.S.C. 102(b) as being anticipated by Artemov, V.A. However, Applicants maintain that Artemov teaches that pyridoxine negates the immunodepressive effect of 6-mercaptopurine when given in optimal doses, which suggests that the method reduces the immunodepressive effect of an immunodepressant, but the study does not show or suggest any methods for preventing, reducing or eliminating the side effects caused by the agent. The Examiner further notes that "no distinction is seen between the terms "immunosuppressive" in the present claims and "immunodepressive" in Artemov's teaching. Because pyridoxine reduced the immunodepressive effect of 6-mercaptopurine, a side effect, . . ." the Examiner maintained the rejection over Artemov. However, as Applicants noted with the Budihardjo citation, Artemov does not disclose, teach nor suggest a method for preventing, reducing or eliminating side effects or neutralizing the side effects of a cancerostatic or immunosuppressive agent administered to a patient, comprising administering a compound having vitamin PP activity as recited in Claim 32 of the present application. For the reasons noted above, Applicants respectfully request that the rejection over Artemov is withdrawn.

Allowance of the claims is respectfully requested.

Respectfully submitted,



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